ORIGINAL ARTICLE

Thyroid Function in Newly Diagnosed HIV-positive Patients

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Abstract

Background: As of 2019, the highest prevalence of human immunodeficiency virus (HIV) in India is seen in the Northeastern states. Endocrine and metabolic disturbances can occur in HIV infection. Thyroid dysfunction is one of the common endocrinopathies. In HIV infection, thyroid function abnormalities are seen in about 4–35% of adult patients. Thyroid function abnormalities range from overt hypothyroidism, subclinical hypothyroidism, and sick euthyroid syndrome to overt hyperthyroidism. Among them, subclinical hypothyroidism is the commonest abnormality. To our knowledge, there have been no studies from Northeastern India done in this regard.

Aims and objectives: To study the thyroid function in newly diagnosed cases of HIV infection attending anti-retroviral therapy (ART) center, Assam Medical College.

To estimate the prevalence and types of thyroid dysfunction in newly diagnosed HIV-infected individuals.

To study thyroid dysfunctions with respect to age, sex, and cluster of differentiation (CD) 4 count.

Materials and methods: Hospital-based observational study was done at a tertiary care centre of upper Assam on newly diagnosed HIV-positive patients who were not started on antiretroviral therapy and who attended the ART centre, Assam Medical College during the period of our study. History, examinations and laboratory investigations, including thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), and CD4 count, are done in all such patients, and only those who fulfilled the inclusion and exclusion criteria of our study are taken as study participants, and their findings tabulated.

Results and observations: A total of 95 newly diagnosed HIV-positive patients fulfilling the inclusion and exclusion criteria of our study were taken. In our study, a total of 36.84% of the patients had thyroid dysfunction. We got subclinical hypothyroidism, overt hypothyroidism, sick euthyroid syndrome, and overt hyperthyroidism as the types of thyroid dysfunction. Among all the types of thyroid dysfunction, subclinical hypothyroidism was the commonest abnormality in our study. Under sick euthyroid syndrome, we got only low FT3 as the biochemical abnormality. Thyroid dysfunctions were more common in females (42.3%) than males (35.8%) and were more common in the age group of 30–39 years. In the present study, among patients with thyroid dysfunction, it was seen that 51.43% of the patients had a CD4 cell count in the range 101–200 cells/mm^3, whereas only 11.43% of patients had a CD4 cell count in the range <50 cells/mm^3 and no patient had a CD4 cell count >500 cells/mm^3.

Conclusion: In our study, we found that thyroid dysfunctions were common in newly diagnosed HIV-positive patients, the prevalence of which was much higher in the general population. Thyroid dysfunction was present in all the stages of the HIV disease.

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Aim

To study the thyroid function in newly diagnosed cases of HIV infection attending ART center, Assam Medical College.

Objectives

- To estimate the prevalence and types of thyroid dysfunction in newly diagnosed HIV-infected individuals.
- To study thyroid dysfunctions with respect to age, sex, and CD4 count.

Introduction

Human Immunodeficiency virus (HIV) is a retrovirus that affects the immune system of the body.[1] HIV is grouped into the genus *Lentivirus* and has two subtypes—HIV-1 and HIV-2. It is HIV-1 which causes most of the infections around the world.[2,3] HIV infection is a global pandemic with significant morbidity and mortality, which has claimed 36.3 million lives so far. Globally in 2020, around 1.5 million people acquired HIV.[1] In the case of India, there are about 23 lakh people living with HIV infection as of 2021.[4] As of 2019, the highest prevalence of HIV in India is seen in the Northeastern states. Though Assam doesn't count as one, it has an annual incidence of 1.33 thousand new infections estimated in 2019.[5] Clinical manifestations in HIV infection are due to immunodeficiency as well as due to the effects of the virus itself.[6] CD4 T cells are selectively infected by HIV. A patient's CD4 count is regarded as a reliable measure of his or her immunologic state.[7,8] Endocrine and metabolic disturbances can occur in HIV infection. Though adrenal insufficiency is the most common HIV endocrinopathy, thyroid dysfunction is also one of the common endocrinopathies.[9] HIV infection and the endocrine system interact in a complex way that ranges from modest biochemical and hormonal abnormalities to overt glandular failure.[10] Thyroid dysfunction can affect multiple systems of the body and can have varied clinical manifestations, which can affect the quality of life. In HIV infection, thyroid function abnormalities are seen in about 4–35% of adult patients.[11–16] Thyroid function abnormalities range from overt hypothyroidism, subclinical hypothyroidism, and sick euthyroid syndrome to overt hyperthyroidism.[9,15] Among them, subclinical hypothyroidism is the commonest abnormality.[13,14,17,18] This is true for both highly active antiretroviral therapy (HAART) naïve and HAART-treated patients[17,19] Numerous studies have suggested that as the disease progresses, thyroid function abnormalities appear. Immunodeficiency correlates with thyroid function abnormalities.[16,20] Though the prevalence of overt glandular failure in HIV patients is similar to that in the general population, the prevalence of subclinical hypothyroidism as well as subtle other biochemical thyroid abnormalities, is high in HIV-infected individuals.[14,15] Numerous studies have demonstrated a relationship between CD4 count, a marker of immunodeficiency in HIV-infected individuals and thyroid dysfunctions.[19,21,22] There have been only a few studies across India from eastern and northern parts of the country which assessed the prevalence and types of thyroid function abnormalities in newly diagnosed HIV-infected patients.[23,24] To our knowledge, there have been no studies from Northeastern India done in this regard.

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Northeastern India consists of the three most highly prevalent states for HIV, and Assam, being surrounded by all these highly prevalent states, receives a considerable number of patients[5] to its various hospitals. This made us think about conducting this study.

Materials and Methods

- Study place: Assam Medical College and Hospital, Dibrugarh.
- Study design: Hospital-based observational study.
- Period of study: The study was conducted over a period of 1 year, from 1st June 2020 to 31st May 2021.

Study Population

All patients who were newly diagnosed as HIV positive at the Integrated and Counseling Testing Centre (ICTC) of Assam Medical College according to the National HIV guidelines and attended the ART centre of Assam Medical College and Hospital, Dibrugarh.

Inclusion Criteria

All cases newly diagnosed as HIV positive at the ICTC center of Assam Medical College and attended the ART centre of Assam Medical College and Hospital, Dibrugarh and were not on antiretroviral therapy.

- Patients with age >12 years.
- Patients willing to give written informed consent.

Exclusion Criteria

- Patients with preexisting diagnosed thyroid disorder with or without treatment or with the presence of thyroid enlargement.
- Patients with coexisting hepatitis B/C coinfection.
- Patients having kidney disease, liver disease, and diabetes mellitus.
- Pregnant patients.
- Patients on drugs known to interfere with thyroid hormones or thyroid function indices.
- Patients who underwent radiation therapy.

Ethical clearance was taken from the Institutional Ethics Committee before starting the study.

Sample Size

Considering a 95% confidence interval with an absolute precision of 10% and a proportion of newly diagnosed HIV-infected individuals with thyroid dysfunction to be 60.4%, as observed in the study by Tripathy et al.,[25] a sample size calculated to be 95 was estimated for the present study.

A detailed clinical history, physical examination, and investigations were conducted in all the consecutive newly diagnosed HIV-infected patients who tested positive at the ICTC centre of Assam Medical College and subsequently attended the ART centre of Assam Medical College. These details were then filled up in a predesigned proforma.

A detailed history of the patients was taken at the time of presentation. Present history was elaborated with an emphasis on symptoms of thyroid disorder (if any) and also the duration of the presenting symptoms. Past history was elaborated with emphasis on any history of thyroid disorder, any presence of neck swelling, any history of diabetes mellitus, any history of liver and kidney disease, any history of opportunistic infections in HIV and malignancies, any history of blood transfusions, radiation therapy, or any surgical procedures. In personal history, subjects were enquired about the risk factors for transmission of HIV, including any use of intravenous drugs. In family history, patients were enquired about the health status of their family members, especially regarding anyone in the family living with HIV/hepatitis B or C positive status. History of intake of thyroxine, antithyroid drugs, antibiotics, anti-tubercular therapy or any drugs which are known to affect thyroid hormones were also enquired about and documented. In female patients, menstrual and obstetrical history was enquired about. A detailed general and systemic examination was done in all the patients with arthrometric measurements and with special emphasis on the presence of any thyroid enlargement and with regard to the various signs of thyroid dysfunction.

Important, relevant pathological investigations, including CD4 cell count; biochemical investigations, including serum TSH, FT3, and FT4; microbiological investigations, including hepatitis B and C serology; radiological investigations, such as chest X-ray, whole ultrasonography abdomen were done, and findings noted. Sputum examination was also done for all the cases.

The subjects who fulfilled the inclusion and exclusion criteria of our study after detailed history, physical examinations and investigations were taken as participants for our study and their clinical and laboratory parameters were tabulated.

Important Definitions

Diagnosis of HIV was made as per the national HIV testing strategies. Three different principles or antigen-based rapid tests were used to confirm the diagnosis. In our institution, all the initial three tests were done as rapid tests. The first test was done using COMBRAIDS dot blot assay, and the second test was by TREDRO HIV 1 and 2 antibody rapid test kit, which uses recombinant antigen.3rd test was done using the VOXPRESS HIV 1 and 2 rapid test kit, which works on the principle of chromatographic lateral flow immunoassay.

In our study, we employed only TSH, FT4, and FT4 as initial tests in all our study participants.

Interpretations of thyroid function test results were made mainly with reference to TSH, FT3, and FT4.[26–29]

Thyroid dysfunctions	*TSH*	*FT4*	*FT3*
Overt Primary hypothyroidism	Elevated	Low	Normal/low
Subclinical hypothyroidism	Elevated	Normal	Normal
Overt Primary hyperthyroidism	Low	Normal/high	High/normal
Subclinical hyperthyroidism	Low	Normal	Normal
Secondary hypothyroidism	Low/normal	Low	Low
Secondary hyperthyroidism	High/normal	High	High

In literature reviews and studies, it was seen that a typical healthy HIV-negative patient has a CD4 count of >500 cells/mm^3, and a CD4 cell count ≤50 cells/mm^3 in HIV patients is associated with substantial mortality and morbidity. CD4 count greater than 500 cells/mm^3 in HIV patients is associated with a lower risk of complications and opportunistic infections. Thus, the CD4 distribution in our study was done with these absolute values of CD4 count in mind.[30]

Laboratory Parameters

Serum Thyroid Stimulating Hormone

Principle used—immunometric with VITROS 5600 immunodiagnostic autoanalyzer system.

Reference range—0.47–4.68 µIU/mL.[31]

Serum Free T3

Principle used—direct competitive immunoassay technique by using VITROS 5600 immunodiagnostic autoanalyzer system.

Reference range—2.77–5.27 pg/mL.[32]

Serum Free T4

Principle used—direct competitive immunoassay technique by using VITROS 5600 immunodiagnostic system.

Reference range—0.78–2.19 ng/dL.[33]

Blood CD4 Count[34]

Technique used—flow cytometry in CD4 easy count kit by using Sysmex Partec Cyflow Counter IVD flow cytometer.

In the case of HIV patients, the absolute number of CD4 cells is more important in assessing the disease progression rather than any reference range of CD4 count calculated in the laboratory.

Statistical Analysis

Data were collected and recorded with predesigned proforma, which were then tabulated to prepare a master chart. The statistical analysis of data was performed using the computer program Statistical Package for the Social Sciences (SPSS) (SPSS for Windows, version 21.0 Chicago, SPSS Inc.) and Microsoft Excel 2019. Results on continuous measurements were presented as mean ± SD.

Results and Observations

A total of 95 newly diagnosed HIV-positive patients fulfilling the inclusion and exclusion criteria of our study were taken, and detailed clinical history, physical examination, and necessary laboratory investigations were done for the evaluation of the patients.

The major findings of the study are summarized below.

The mean age in our study was found to be 35.85 ± 8.89 years, with the most common age group being 30–39 years (Fig. 1).

In our study, the majority of the patients were male. The male-female ratio was 2.39:1 (Fig. 2).

In our study, mean ± standard deviation (SD) of the CD4 distribution, FT3, FT4 and TSH values was 230.82 ± 144 cells/mm^3, 3.71 ± 1.13 pg/mL, 1.62 ± 0.54 ng/mL, and 3.91 ± 2.75 µIU/mL, respectively.

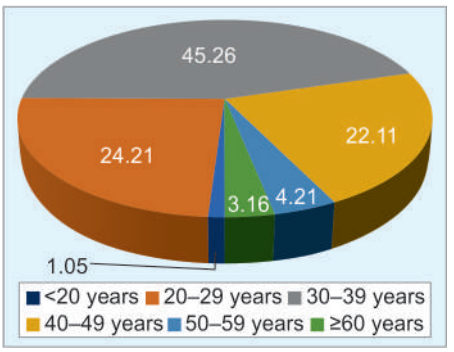

Fig. 1: Age-wise distribution

The maximum number of patients had a CD4 cell count in the range of 201–300 cells/mm^3 (Fig. 3).

In our study, a total of 36.84% of the patients had thyroid dysfunction (Fig. 4).

We got subclinical hypothyroidism, overt hypothyroidism, sick euthyroid syndrome and overt hyperthyroidism as the types of thyroid dysfunction. Among all the types of thyroid dysfunction, subclinical hypothyroidism was the commonest abnormality in our study, followed by sick euthyroid syndrome and, subsequently, overt hypothyroidism and hyperthyroidism. None of the patients with thyroid dysfunction, including overt hypo and hyperthyroidism, had any signs and symptoms of thyroid dysfunction at the time of the study.

In our study, among the patients with thyroid dysfunction, 71.43% of the patients had subclinical hypothyroidism (i.e., 26.31% of all our study participants). A total of 8.57% of the patients had overt hypothyroidism (i.e., 3.16% of all our study subjects). 2.86% of the patients had overt hyperthyroidism (i.e.,1.05% of all our study subjects). Around 17.14% of the patients had sick euthyroid syndrome (i.e., 6.32% of all our study subjects). Under sick euthyroid syndrome, we got only low FT3 as the biochemical abnormality.

Thyroid dysfunctions were more common in females (42.3%) than males (35.8%).

Types of thyroid dysfunction	*Number of Males*	*Number of females*	*Total number of patients (n)*	*Percentage*
Overt hypothyroidism	3	0	3	8.57
Subclinical hypothyroidism	15	10	25	71.43
Overt hyperthyroidism	1	0	1	2.86
Subclinical Hyperthyroidism	0	0	0	0.00
Sick euthyroid syndrome (low FT3)	5	1	6	17.14
Secondary hypothyroidism	0	0	0	0.00
Secondary hyperthyroidism	0	0	0	0.00
Total	24	11	35	100

Types of thyroid dysfunction	*Patients with age group (in years) (n)*						
	<20	*20–29*	*30–39*	*40–49*	*50–59*	*≥60*	*Total*
Overt hypothyroidism	0	0	2	0	0	1	3
Subclinical hypothyroidism	0	6	12	6	1	0	25
Overt hyperthyroidism	0	0	0	0	0	1	1
Subclinical Hyperthyroidism	0	0	0	0	0	0	0
Sick euthyroid syndrome (low FT3)	0	0	3	3	0	0	6
Secondary hypothyroidism	0	0	0	0	0	0	0
Secondary hyperthyroidism	0	0	0	0	0	0	0
Total	0	6	17	9	1	2	35

Types of thyroid dysfunction	*Patients with CD4 cell count (cells/mm^3) (n)*							
	≤50	*51–100*	*101–200*	*201–300*	*301–400*	*401–500*	*>500*	*Total*
Overt hypothyroidism	2	1	0	0	0	0	0	3
Subclinical hypothyroidism	2	6	15	0	1	1	0	25
Overt hyperthyroidism	0	0	0	0	1	0	0	1
Subclinical Hyperthyroidism	0	0	0	0	0	0	0	0
Sick euthyroid syndrome (low FT3)	0	2	3	0	1	0	0	6
Secondary hypothyroidism	0	0	0	0	0	0	0	0
Secondary hyperthyroidism	0	0	0	0	0	0	0	0
Total	4	9	18	0	3	1	0	35

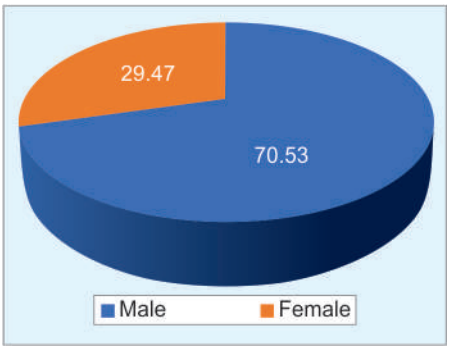

Fig. 2: Gender-wise distribution

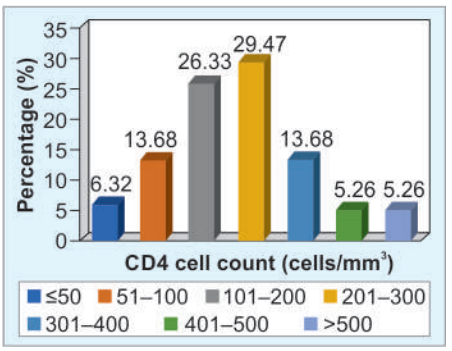

Fig. 3: Cluster of differentiation (CD4) cell distribution

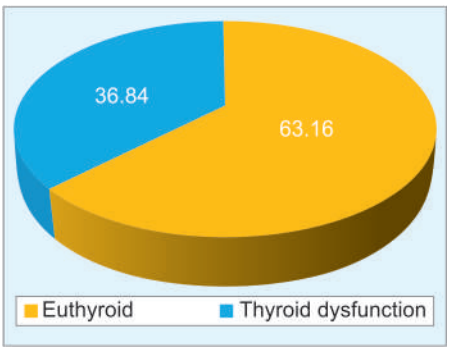

Fig. 4: Thyroid function status

In our study, in the case of patients with thyroid dysfunction, the majority (48.57%) of the patients were in the age group of 30–39 years.

In our study, out of the patients with thyroid dysfunction, 51.43% of patients had a CD4 cell count in the range of 101–200 cells/mm^3.

Discussion

In our study, 36.84% of the patients had thyroid dysfunction. We got subclinical hypothyroidism, overt hypothyroidism, sick euthyroid syndrome and overt hyperthyroidism as types of thyroid dysfunction., among which subclinical hypothyroidism was the commonest abnormality. Thus, it can be seen that the prevalence of thyroid dysfunction was more in HIV-positive patients as compared to the general population, where it is 5% in women and 0.5% in men.[35] Even comparing a population-based study in India, which estimated thyroid dysfunction as high as 19%,[36] our study found a higher prevalence of thyroid dysfunction in HIV patients. Saha et al.,[23] in their observational study on newly diagnosed HIV-positive patients conducted in India, found similar prevalence and similar types of thyroid dysfunctions except for sick euthyroid syndrome. They also found subclinical hypothyroidism to be the commonest. However, Dev et al.,[18] in their study on newly diagnosed HIV-positive patients done in India, found a higher prevalence of thyroid dysfunctions but with similar types except for overt hyperthyroidism. They also found subclinical hypothyroidism to be the commonest. Variation in pattern and prevalence may be due to the selection of patients with different rates of disease progression, other comorbid conditions and different clinical stages in different studies.

Among patients with thyroid dysfunction, 26.31% of the study participants had subclinical hypothyroidism. Saha et al.,[23] Meena et al.,[37] and Dev et al.[18] in their studies observed similar results. 3.16% of the patients had overt hypothyroidism. This is similar to that observed in the studies done by Midha et al.,[24] Noureldeen et al.[38] 1.05% of the patients had overt hyperthyroidism. This is similar to the observations made by Noureldeen et al.[38] In European studies done on the general population, overt hyperthyroidism was 0.8% in women and 0.48% in men.[39] So, the prevalence of hyperthyroidism found in HIV patients is not much different from what is observed in the general population. 6.32% of the patients had sick euthyroid syndrome. In sick euthyroid syndrome, we got only low FT3 as the biochemical abnormality. This is similar to the studies done by Noureldeen et al.[38] and Dev et al.[18]

In our study, thyroid dysfunctions were more common in females than males in our study. This finding is similar to the observations made in the general population, where thyroid dysfunctions, in general, are seen more commonly in females than males.[35] In the studies by Quirino et al.[17] and Vohra et al.,[40] it was seen that thyroid dysfunctions were more common in females than males. However, Saha et al.,[23] in their study found no association of gender with any of the thyroid dysfunctions. Thus, large case-control studies are needed to ascertain the association of gender with thyroid dysfunction.

In our present study, 48.57% of the patients with thyroid dysfunction were aged between 30 and 39 years. In studies by Parihar et al.[21] and Vohra et al.,[40] similar findings were noted. However, Saha et al.[23] and Nelson et al. [41] in their studies found no association of age with thyroid dysfunctions. Thus, large case-control studies are needed to ascertain the association of age with thyroid dysfunction.

In the present study, among patients with thyroid dysfunction, it was seen that 51.43% of the patients had a CD4 cell count in the range of 101–200 cells/mm^3, followed by 25.71% of patients in the CD4 cell count range 51–100 cells/mm^3 whereas only 11.43% patients had CD4 cell count in the range <50 cells/mm^3 and no patient had a CD4 cell count >500 cells/mm^3. In the case of overt hypothyroidism, 66.66% of the patients had CD4 cell counts ≤50 cells/mm^3. In the case of subclinical hypothyroidism, 60% of the patients had a CD4 cell count in the range of 101–200 cells/mm^3. In the case of sick euthyroid syndrome, 50% of the patients had a CD4 cell count in the range of 101–200 cells/mm^3. In studies by Saha et al.[23] and Parihar et al.,[21] they found the majority of the patients with thyroid dysfunction had a CD4 cell count below 250 cells/mm^3. They also observed that most of the patients with subclinical hypothyroidism had a CD4 cell count below 250 cells/mm^3.In studies by Ji et al.[16] and Sachdeva et al.,[42] it was observed that the CD4 cell counts in cases of overt hypothyroidism were the lowest among all other thyroid dysfunctions. They also showed that CD4 cell counts were high in cases of hyperthyroidism when compared with hypothyroidism. However, a prospective study by Nelson et al.[41] done on HIV patients had not found any association between thyroid function and CD4 cell counts.

Conclusion

In our study, we found that thyroid dysfunctions were common in newly diagnosed HIV-positive patients, the prevalence of which was much higher in the general population. Thyroid dysfunction was present in all the stages of the HIV disease. We found subclinical hypothyroidism, overt hypothyroidism, overt hyperthyroidism, and sick euthyroid syndrome as the principal types, among which subclinical hypothyroidism was the most common.

Low CD4 cell count was an important indicator of the risk of thyroid dysfunction in our study. Thyroid dysfunction, which may be subclinical in the early stages of the disease, may become overt and symptomatic with the fall of CD4 cell count.

As subclinical hypothyroidism remains the most common thyroid abnormality in patients with HIV infection, we recommend screening thyroid function in patients with HIV infection with severe immunodeficiency. HIV is here

to stay, but we should aim that individuals should be free of any morbidity owing to the complications like thyroid dysfunctions. Thus, we should invest our efforts to improve the quality of life.

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